Infectious Disease Updates for Primary Care

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KEYWORDS

• RSV • Influenza • COVID-19 • Vulvovaginal candidiasis • DoxyPEP

KEY POINTS

- Respiratory syncytial virus threatens infants and older adults, but new vaccines and a monoclonal antibody provide protection.
- Seasonal influenza remains a public health menace, but immunizations and antivirals may reduce risk of severe disease.
- COVID-19 still afflicts thousands of Americans every day—immunizations for all, and antivirals for those at highest risk, can help save lives.
- In men who have sex with men and transwomen, doxycycline taken after condomless sex may dramatically reduce the risk of syphilis and chlamydia.
- Women suffering from drug-resistant vulvovaginal candidiasis now have a safe, effective treatment option.

INFECTIOUS DISEASE UPDATES FOR PRIMARY CARE

The last year has brought exciting developments in the prevention and treatment of infectious diseases for primary care: new vaccines to prevent respiratory syncytial virus (RSV), influenza, and COVID-19; a new treatment of drug-resistant vaginal yeast infections; and—despite the increasing incidence of bacterial sexually transmitted diseases (STDs)—we also have exciting news about repurposing an old antibiotic for prevention.

RESPIRATORY VIRUS UPDATES

Introduction

Primary care providers are the front line in caring for patients with acute respiratory infections—and are also ideally positioned to help prevent them. Internists are more likely to assess vaccination status and to recommend and stock vaccines than

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SHOUT
SHARE
IT

subspecialists.[1] Internists provide around half of all vaccination services among Medicare patients.[2] Outpatient visits for influenzalike illness account for tens of millions of outpatient visits annually.[3,4] Although the burden of illness from respiratory viruses is significant, new developments in the field provide novel measures to prevent and treat these infections.

Respiratory syncytial virus

RSV is a familiar nemesis to pediatricians, as it is the leading cause of hospitalization among US infants.[5] But it has only recently gained attention for its role in causing morbidity and mortality among adults, particularly elderly individuals and those with cardiac or pulmonary comorbidities.[6,7] Multiple studies have demonstrated a similar burden of illness from RSV and influenza,[8–10] but until recently there were no vaccines for RSV. Fortunately, new tools to protect patients from RSV have been developed (**Fig. 1**).

Prevention of respiratory syncytial virus in older adults

In 2023, the Food and Drug Administration (FDA) approved two new protein-based vaccines for RSV for adults older than 60 years. Both were shown in large phase 3 trials to be well tolerated and efficacious in preventing symptomatic RSV lower respiratory tract disease (**Table 1**).[11] A messenger RNA (mRNA) RSV vaccine is also in development, with preliminary phase 2 to 3 trial results demonstrating this vaccine to be safe and similarly efficacious (see **Table 1**).[12]

Regarding adverse events related to RSV vaccination, two categories of severe adverse events are noted for both the Pfizer and GSK vaccine products, although the absolute number of events in each of these categories was extremely small. First, both trials observed an increased number of participants with atrial fibrillation in the vaccine group, including some individuals with new-onset atrial fibrillation, although the numbers were too small to make definitive conclusions about the relationship between atrial fibrillation and the RSV vaccine. Second, trials for both vaccines observed three cases of inflammatory neurologic events, including Guillain-Barré syndrome and acute disseminated encephalomyelitis (ADEM), in individuals who received the vaccine (see **Table 1**). Both atrial fibrillation and inflammatory neurologic events will be monitored in postmarketing surveillance for both products. Until more is known about the frequency and causality of these rare adverse events, patients should be informed that these complications were seen in the vaccine trials, but at very low rates (<0.02%), and that the risk of these adverse events must be weighed against the patient's risk of severe RSV disease. Thus, rather than make a blanket recommendation for RSV vaccination among all individuals in a certain age group or risk category, the Advisory Committee on Immunization Practices (ACIP) recommended that the

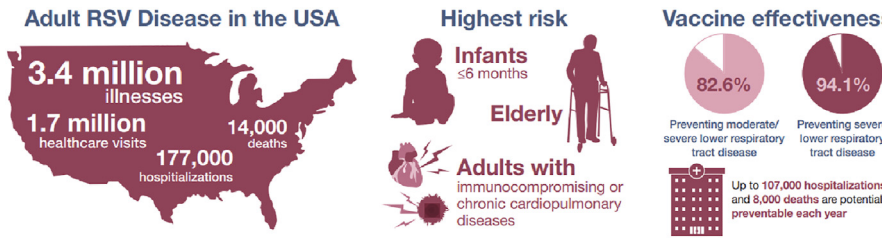

Fig. 1. Overview of RSV in America. (*From* Falsey AR, Walsh EE. Respiratory syncytial virus Prefusion F vaccine. Cell. 2023 Jul 20;186(15):3137–3137.e1. https://doi.org/10.1016/j.cell.2023.05.048. PMID: 37478816.)

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Table 1
Vaccines for respiratory syncytial virus in older adults

	Arexvy (GSK)	Abrysvo (Pfizer)	mRNA-1345 (Moderna)
FDA approved at time of writing	Yes	Yes	No
Vaccine type	Adjuvanted protein–based vaccine	Unadjuvanted bivalent protein–based vaccine	mRNA vaccine
Age	Adults ≥ 60	Adults ≥ 60	Adults ≥ 60
Dosing	Single dose	Single dose	Single dose
Vaccine efficacy[a]	82.6%	85.7%	83.7%
Serious adverse events	No difference between vaccine and placebo	No difference between vaccine and placebo	No difference between vaccine and placebo
Unsolicited adverse events	Increased incidence of atrial fibrillation in vaccine group	Increased incidence of atrial fibrillation in vaccine group	—
Inflammatory neurologic events	2–3[b] events among 17,992 participants	3 events among 18,622 participants	None among 17,793 vaccinated participants

[a] Vaccine efficacy defined as efficacy against symptomatic, lab-confirmed lower respiratory disease with ≥ 2 or ≥ 3 signs/symptoms.
[b] Three events were initially reported; one was subsequently reclassified as being due to hypoglycemia and dementia rather than ADEM.[11]

decision to immunize a patient against RSV be made via a process of shared clinical decision-making, taking into account the patient's preferences and risk for severe illness.[11]

Respiratory syncytial virus prevention in infants

Before 2023, the only pharmacologic tool for RSV prevention in infants was palivizumab, a monoclonal antibody requiring monthly intramuscular injections throughout the RSV season. Because of its high cost and frequent dosing requirements, its use was limited to only the highest-risk infants. In 2023, nirsevimab, a new long-acting monoclonal antibody, was approved for prevention of RSV lower respiratory tract disease in infants as a one-time dose (**Table 2**). Because of the high efficacy, safety, and cost-effectiveness of nirsevimab compared with palivizumab, the ACIP recommends nirsevimab for all infants aged younger than 8 months who are born during or entering their first RSV season.[13]

In addition to nirsevimab, a second new measure was approved in 2023 for prevention of RSV lower respiratory disease in infants: Abrysvo, the same Pfizer RSV vaccine described earlier, given to expecting mothers during pregnancy. A trial of this vaccine in pregnancy demonstrated vaccine efficacy against medically attended severe lower respiratory tract illness in infants of 81.8% in the first 90 days after birth and 69.4% in the first 180 days (see **Table 2**).[14] Vaccine efficacy against medically attended RSV-associated lower respiratory tract illness in the first 90 days was 57.1%. In the trial, the vaccine was administered between 24 and 36 weeks gestation, and people at increased risk of preterm birth were excluded. Although it did not reach statistical significance, in the trial there were more preterm births, preeclampsia, low-birth-weight infants, and neonatal jaundice in the vaccine group compared with placebo. Postmarketing surveillance of preterm birth and hypertensive disorders of pregnancy is

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Table 2
Respiratory syncytial virus prevention in infants

	Palivizumab	Nirsevimab	Abrysvo (Pfizer)
Mechanism	Passive immunization—monoclonal antibody	Passive immunization—monoclonal antibody	Immunization of birth parent during pregnancy
Dosing	Monthly during RSV season	Single dose prior to, or at the start of, RSV season	Single dose at 32–36 wk gestation
Administration	Intramuscular	Intramuscular	Intramuscular
Target population	Highest-risk infants	• All infants younger than 8 mo entering their first RSV season • Infants 8–19 mo old at increased risk of severe RSV entering their second RSV season	Pregnant people at 32–36 wk gestation
Efficacy	39%–78% reduction in hospitalization resulting from RSV[15]	79.0% vs medically attended RSV LRTI; 80.6% efficacy vs RSV LRTI hospitalization	81.8% vs severe LRTI in first 90 days 69.4% vs severe LRTI in first 180 days
Adverse effects	No significant difference from placebo	No significant difference from placebo	Potential increased risk of preterm birth and hypertensive disorders of pregnancy

planned, and the FDA approval specifies a dosing interval of 32 to 36 weeks to reduce the risk for preterm birth.

Protecting infants from respiratory syncytial virus—the bottom line

In the past year, the approvals of nirsevimab for infants and maternal immunization with Abrysvo have provided dramatic advances in infant RSV prevention. The two have not been compared head-to-head, but both provide moderate to high efficacy against severe RSV in young infants. The choice to use infant monoclonal vs maternal immunization will likely depend on cost and logistical considerations, which may differ across health systems. In situations where both are available, patients and providers may choose nirsevimab due to its more favorable side-effect profile. But, some birth parents may wish to receive an injection themselves, rather than have their infant require another injection after delivery. In either case, this is a choice of one product or the other: there is no recommendation to administer both products to protect the same child.

Diagnostics

The gold-standard test for RSV is reverse transcription polymerase chain reaction (RT-PCR) of a nasal or nasopharyngeal swab. Other commonly used tests are less sensitive and may lead to underdiagnosis: in adults, the sensitivity of rapid antigen testing compared with RT-PCR is 64%.[16] Ideally, testing of symptomatic patients would include multiplex testing for SARS-CoV-2 and influenza, as respiratory viral infections

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may be difficult to distinguish from one another based on symptoms alone.[17] Home-based self-testing for RSV has not yet been approved but is in development.[18]

Treatment

Unfortunately, although great advances have been made in RSV prevention, the mainstay of treatment continues to be supportive care. Studies of novel antivirals are ongoing. This makes protection of vulnerable patients through vaccination or monoclonal antibody administration all the more critical.

Challenges and areas of uncertainty

Although the development of new vaccines and monoclonals for RSV represent a tremendous step forward for RSV prevention, several areas of uncertainty remain.

- The durability of the RSV vaccine response is unknown, and whether booster doses will be needed over time has not yet been determined.
- There is scant data regarding simultaneous administration of either RSV vaccine with vaccines for influenza, SARS-CoV-2, and other indications for this age group, such as the recombinant zoster vaccine (Shingrix by GSK) and pneumococcal vaccines. Early data suggested the possibility of slightly decreased influenza immune response when coadministered with RSV,[11] whereas a subsequent study demonstrated that coadministration of influenza and RSV vaccination was safe and noninferior to administration of each vaccine alone.[19]
- Although both RSV vaccines for older adults demonstrated protection against symptomatic, lab-confirmed lower respiratory disease, these studies were not powered to provide data on efficacy against hospitalization, intensive care unit admission, or death—key metrics in understanding the value of these novel immunizations.
- With vaccine fatigue[20,21] and high levels of vaccine-related misinformation over the course of the COVID pandemic,[22] it remains to be seen how widely RSV vaccines will be used and in particular whether they will be used by the patients most vulnerable to severe disease. At the time of writing, only 17% of US adults older than 60 years have received an RSV vaccine.[23]

Influenza

Prevention

Trivalent and quadrivalent vaccines. Annual influenza vaccines are formulated to include the strains most likely to be circulating during the upcoming influenza season. Previously, the seasonal influenza vaccine was trivalent and included two influenza A strains and one influenza B strain; circulation of two influenza B strains prompted the addition of a second influenza B strain, making a quadrivalent vaccine. Trivalent vaccines were phased out in 2021 to 2022 period, with all available influenza vaccines in the United States being quadrivalent since then. However, with the shifting epidemiology of respiratory viruses during the SARS-CoV-2 pandemic, the influenza B/Yamagata strain has not been seen since March 2020. The World Health Organization and FDA have recommended that this strain be removed from future influenza vaccines; the timeline for this change is unclear.[24]

Adjuvanted, high-dose, and recombinant vaccines. Aging is associated with a decline in immune function, with increased vulnerability to infections and decreasing response to vaccinations.[25] Given the need for improved protection against influenza in elderly populations, several effective vaccine strategies have been developed for use in this age group.

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The ACIP recommends that adults older than 65 years receive either high-dose inactivated influenza vaccine, recombinant influenza vaccine, or adjuvanted inactivated influenza vaccine. Large trials comparing standard dose with enhanced vaccines for older adults have demonstrated 12% to 30% higher relative efficacy for high-dose and adjuvanted vaccines.[26–29] However, if none of these is available at the time of immunization, a standard dose influenza vaccine can be given instead. Of note: a recent study also demonstrated superiority of the high-dose recombinant vaccine, compared with standard dose, in adults aged 50 to 64 years,[30] raising the possibility that in the future, high-dose vaccines could become recommended for populations younger than 65 years as well, if additional studies support this finding.

Egg allergies. Most influenza vaccines are produced in chicken eggs. Thus, until recently, individuals with severe egg allergy (symptoms other than urticaria) were recommended to be vaccinated in a medical setting "supervised by a health care provider who is able to recognize and manage severe allergic reactions." Thankfully, this is no longer the case: current ACIP guidance indicates that no additional safety precautions are needed for influenza vaccination based on an egg allergy alone, regardless of severity.[31] This recommendation is based on a significant body of evidence demonstrating that administration of live and inactivated influenza vaccines is safe in recipients with egg allergy, including those with anaphylaxis.[32]

Diagnostics

Outpatient diagnosis of influenza infection. The most recent Centers for Disease Control and Prevention guidelines for influenza recommend choosing molecular testing (PCR, nucleic acid amplification test) over rapid antigen tests whenever possible, due to low sensitivity of antigen testing.[33]

Home-based self-testing. Home-based self-swabbing for respiratory virus testing became commonplace during the SARS-CoV-2 pandemic. Until recently, testing was available only for SARS-CoV-2. However, a home-based molecular test has now been FDA approved for SARS-CoV-2 and influenza, and home-based self-testing for RSV is in development.[18] Uptake of novel tests for multiple viruses will likely depend on cost, insurance coverage, availability, and provider awareness.

Treatment

Oseltamivir remains the standard of care for treatment of influenza in most cases (**Table 3**). In 2018 baloxavir was approved in for treatment of influenza A and B infections and is another option for outpatient therapy with comparable efficacy.[34] Baloxavir is a first-in-class influenza antiviral with an enticing feature: treatment consists of just a single dose. Although there is a greater body of literature supporting the use of oseltamivir, baloxavir could be considered in certain clinical situations, such as when a single-dose regimen is needed or the patient has a history of intolerance to oseltamivir (see **Table 3**). There is also some evidence for superiority of baloxavir compared with oseltamivir for influenza B infection,[35] suggesting that preferential use in these cases may be helpful.

Influenza challenges and uncertainties

- Because of concerns for the prognosis of patients experiencing severe influenza infection and for possibility of antivirals driving drug resistance, the question has been raised whether using combination therapy would improve outcomes and/or mitigate this risk.[38] A randomized trial was conducted to answer this question but found that the combination of baloxavir plus a neuraminidase inhibitor did not improve outcomes compared with a neuraminidase inhibitor alone.[39] As a result,

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Table 3
Outpatient treatment and postexposure prophylaxis for influenza

	Oseltamivir	Baloxavir
Key treatment populations	• Pregnant people • Hospitalized patients • Immunocompromised patients	• Concerns about ability to adhere to 5-day course of oseltamivir • History of adverse reaction to oseltamivir • Consider for influenza B infection—some evidence for greater efficacy than oseltamivir[35]
Dosing schedule—treatment	5-day course	Single dose
Price (approximate) for a course of treatment	$50–100 for 5-day course (generic)	$160–210 for a single dose
Most common adverse effects	Nausea, vomiting, headache	Diarrhea
Contraindications	—	Should not be used in highly immunocompromised patients due to development of resistance
Postexposure prophylaxis	• Begin within 48 hours of influenza exposure • 7-day course of once-daily dosing after last known influenza exposure	• Begin within 48 hours of influenza exposure • Single dose

Of note, although the 2011 CDC guidance suggested using double-dose oseltamivir (150 mg BID) in severely ill patients, studies have not shown benefit,[36,37] and the 2018 CDC guidelines for treatment of influenza indicate that higher doses of oseltamivir should not be routinely used.[33].

combination therapy with oseltamivir and baloxavir is not currently recommended for the routine treatment of influenza.

- Another area of uncertainty is around coadministration of vaccines for influenza, SARS-CoV-2, and RSV. Present ACIP guidance is that influenza and SARS-CoV-2 vaccines can be given at the same time, ideally in different limbs; the ACIP also indicates that the coadministration of the RSV vaccine with other vaccines is acceptable, while acknowledging that data are limited and evolving.[31]

SARS-CoV-2

Prevention

Updated 2023 to 2034 COVID-19 vaccines replaced the original and bivalent COVID vaccines. The 2023 to 2024 updated vaccine targets the XBB lineage of the Omicron variant and is more closely matched to currently circulating strains than prior versions of the vaccine. Vaccine schedules have been updated and simplified, so that receipt of a single dose of an updated COVID-19 mRNA vaccine, or two doses of a Novavax COVID-19 vaccine, is now considered fully vaccinated. In the past 2 years, however, uptake of updated vaccines has been poor, with approximately 20% of US adults receiving the 2022 to 2023 bivalent booster.[40] As of 12/1/2023, only 16% of US adults had received the 2023 to 2024 updated COVID vaccine.[41]

Diagnostics

Since the end of the official public health emergency, COVID-19 testing has become less available, with access to molecular testing (PCR) being particularly limited. Rapid antigen

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tests are now widely available and have shown to be reliable for detecting the Omicron variant.[42,43] However, newer data suggest that early antigen testing may be less sensitive than it was earlier in the pandemic in populations with high rates of prior COVID-19, high rates of vaccination, or both.[44] Specifically, viral loads were found to peak at day 4 to 5 after symptom onset, with peak antigen test sensitivity on day 4. Therefore, it should be emphasized that the sensitivity of antigen testing early in the course of illness is low and that SARS-CoV-2 should not be considered "ruled out" in patients with compatible symptoms and negative antigen testing soon after symptom onset.

Treatment

A full review of the treatment of COVID-19 is beyond the scope of this article. In general: as of early 2024, because of the virulence attenuation of commonly circulating strains of SARS-CoV-2, primary care providers can thoughtfully recommend antiviral treatment of patients who are at risk of infection complications, especially those who are older than 60 years, those who are immunosuppressed, and those with chronic cardiopulmonary conditions. These patients comprise most of the 1000 to 1500 Americans who currently die of COVID-19 each week. Younger, otherwise healthy patients will almost always recover from a self-limited illness and may reasonably choose not to take antivirals. Thorough guidelines can be found on the NIH Covid Treatment Guidelines Web site https://www.covid19treatmentguidelines.nih.gov/, which includes information on outpatient evaluation, triage, and follow-up. Following is a brief summary of outpatient antivirals for patients who do not require supplemental oxygen.

Ritonavir-boosted nirmatrelvir (Paxlovid). Ritonavir-boosted nirmatrelvir is the preferred therapy for nonhospitalized patients with COVID-19 and is currently given as a 5-day course.[45] In high-risk patients treated within 3 days of symptom onset, nirmatrelvir/ritonavir (n/r) demonstrated a relative risk reduction in COVID-19–related hospitalization or death by 89%.[46] However, it is a strong CYP3A inhibitor and has significant interactions with several other drugs, which may preclude its use in some individuals. Some of these drug interactions can produce life-threatening side effects; therefore, drug interactions should be checked in all patients before treatment initiation. The University of Liverpool provides a useful tool for checking for drug interactions: https://www.covid19-druginteractions.org/checker.

However, many drug interactions can be mitigated by briefly holding or reducing doses of concomitant medications. For instance, statins, which are commonly prescribed medications in older patients with cardiovascular risk factors—a group of patients at higher risk for complications of COVID-19—interact with nirmatrelvir/ritonavir, but adverse effects from this drug interaction can be avoided as outlined in **Table 4**.

Remdesivir. For patients who cannot receive nirmatrelvir/ritonavir due to drug interactions or other reasons, the next best therapy is a 3-day course of remdesivir.[45] A randomized, double-blind, placebo controlled trial of nonhospitalized patients with COVID-19 and at least one risk factor for disease progression demonstrated that a 3-day course of intravenous remdesivir resulted in an 87% lower risk of hospitalization or death, compared with placebo.[47]

Molnupiravir. If patients cannot take nirmatrelvir/ritonavir, and remdesivir not feasible or otherwise contraindicated, high-risk patients can be prescribed molnupiravir.[45] Among nonhospitalized, high-risk, unvaccinated adults, molnupiravir reduced the risk of hospitalization or death from 9.7% to 6.8%.[48] However, a subsequent study among vaccinated high-risk adults did not show a reduction in hospitalization or death with molnupiravir.[49]

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Table 4
Drug interactions between statins and nirmatrelvir/ritonavir and strategies for mitigation

Statin	Effect	Situations Where It is Safe to Stop Statin (Such as Primary Prevention)	Situations Where It is Unsafe to Stop Statin (eg, Recent Mi, Secondary Prevention)
Atorvastatin	Increased atorvastatin levels due to inhibition of CYP3A4 by n/r	Stop atorvastatin during n/r; restart 3 days after the last dose	Reduce atorvastatin dose to 10 mg daily during n/r; resume normal dose 3 days after completing n/r
Rosuvastatin	Increased rosuvastatin levels due to ritonavir inhibition of drug transporters	Stop rosuvastatin during n/r (5 days)	Decrease dose to 10 mg/day during coadministration with n/r (5 day)
Simvastatin Lovastatin	Massive increase (100-fold) in simvastatin and lovastatin levels; increased risk of toxicity including rhabdomyolysis	Stop simvastatin or lovastatin at least 12 hours before starting n/r Resume 5 days after completing n/r. Concurrent administration of n/r with simvastatin or lovastatin is **contraindicated.**	Stop simvastatin or lovastatin at least 12 hours before starting n/r Resume 5 days after completing n/r. Concurrent administration of n/r with simvastatin or lovastatin is **contraindicated.**
Pravastatin	No interaction	No change	No change

Adapted from https://www.acc.org/-/media/Clinical/PDF-Files/Approved-PDFs/2022/06/24/19/07/COVID-Drug-Clinical-Bulletin.pdf. *Adapted from* https://www.covid19-druginteractions.org/checker; *Adapted from* https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217188s000lbl.pdf

Challenges and areas of uncertainty

Rebound. Although there is substantial evidence that people can experience viral and symptomatic rebound during the course of COVID-19, studies of whether this is associated with antiviral use have produced mixed results.[50,51] Although a causal role for antivirals in rebound remains to be elucidated, there is consensus that concerns about rebound should not prevent the use of antivirals in appropriate patients and that high-risk patients benefit from antiviral therapy, particularly when it is initiated early in the course of infection.[45] Whether a second course of Paxlovid for people with rebound symptoms and viremia could be effective is unknown; clinical trials are underway.[52,53]

Treatment duration. Although nirmatrelvir/ritonavir (Paxlovid) is approved as a 5-day treatment course, and this has been shown to be effective in general patient populations, there is concern that this treatment duration is insufficient in immunocompromised patients, who may experience prolonged viral replication.[54,55] A clinical trial in immunocompromised patients to compare 5, 10, and 15 days of nirmatrelvir/ritonavir is ongoing.[53]

Long COVID/postacute sequelae of COVID-19. The effects of COVID-19 may linger for months or longer. These postacute sequelae of COVID-19 (PASC) may involve any combination of body systems, often including debilitating fatigue. A substantial portion of Americans experience a constellation of issues long after their respiratory infection has resolved. In 2022, approximately 8% of respondents to a large survey

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indicated that they had experienced PASC, with highest burden among Hispanic respondents.[56] PASC can happen to anyone, but risk factors include unvaccinated status, older age, severe infection, and immunosuppression. The best way for patients to reduce risk of PASC is to be immunized with the latest vaccine. We have hoped that prompt antiviral treatment would reduce the risk of PASC, but this was not found in a recent survey of COVID-19 survivors.[57] No medications have FDA approval for the treatment of PASC. This condition may be very debilitating and discouraging for patients and doctors alike. The CDC offers an online resource that includes linkages to observational and clinical trials that all patients should consider joining: https://covid19.nih.gov/covid-19-topics/long-covid.

VAGINAL YEAST INFECTIONS

Vulvovaginal candidiasis (VVC) is a common complaint among women in primary care, especially among those who have recently taken antibiotics. *Candida albicans* is the leading cause, which is fortunate because most *C albicans* remains susceptible to first-line treatment. Patients usually respond promptly to treatment with a single dose of oral fluconazole or a course of topical triazole cream (eg, clotrimazole). When patients fail to improve, two main explanations should be considered:

First, the diagnosis of VVC should be confirmed. Understandably, women may mistake another vaginal discharge syndrome for "yeast." Impostors include bacterial vaginosis and sexually transmitted infections such as trichomoniasis and gonorrhea—none of which will respond to triazoles.

Second, if VVC is confirmed, fluconazole resistance should be ruled out using culture and sensitivity of a vaginal swab or fluid specimen. Often, Candida species such as glabrata will be partially resistant to fluconazole and the topical triazoles—these cases can be stubborn and often require repeated courses of compounded or OTC boric acid suppositories. In 2022, the FDA approved a new treatment option for these patients: ibrexafungerp. This is a novel triterpenoid antifungal that blocks glucan synthesis in most yeast species, including *Candida glabrata*. Prescribers may think of this as an "oral echinocandin." A 1-day course is highly efficacious in most women suffering from drug-resistant VVC, and the drug is well tolerated (with gastrointestinal upset in 10%–15% of patients).[58] Ibrexafungerp should only be used when first-line treatments have failed, not only to preserve their spectrum of activity over time but also because of the high cost of this medication, approximately $500 to $600.

SEXUALLY TRANSMITTED INFECTION PREVENTION USING DOXYCYCLINE

The incidence of sexually transmitted infections (STIs) such as syphilis, chlamydia, and gonorrhea has increased strikingly in recent years.[59] Two recent studies demonstrated a substantial reduction in risk of these bacterial infections among men who have sex with men and transgender women, by simply taking a dose of doxycycline after condomless sex. In the DoxyPEP trial,[60] people with elevated risk of acquiring STIs (some living with HIV, others participating in HIV preexposure prophylaxis) were randomized to swallow 200 mg of doxycycline postexposure prophylaxis within 72 hours following condomless sex or to receive usual care. Both groups underwent STI testing at least every 3 months and were followed-up for a year. The overall incidence of a bacterial STI among doxycycline recipients was 24% versus 48% among those receiving standard of care. Another trial called Doxyvac[61] reached similar conclusions. Based on these findings, the CDC encourages primary care providers to discuss benefits and risks of this strategy with their patients.[62] Some talking points to consider are as follows:

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- Doxycycline postexposure prophylaxis (PEP) should be taken within 24 hours of condomless sex if at all possible—there may still be benefit if taken any time within 72 hours. Benefits beyond that time are unlikely.
- Even in the doxycycline PEP arm, there was still an alarmingly high (although lower) rate of STIs. In other words, doxycycline PEP was beneficial but certainly not perfect. Therefore, men who have sex with men and transgender women who try it should continue to be carefully monitored for STI acquisition, including screening at least every 3 months.
- Cisgender women and men who have sex with women were not included in these trials. Unfortunately, a well-designed trial focused on protecting women at high risk from STIs using the same protocol recently failed to detect benefit.[63] If such patients are eager to try this technique, that decision can be individualized in light of specific risk factors and preferences, but they should understand that current evidence is against this practice.
- Either doxycycline monohydrate or hyclate may be used. In either case, patients should avoid consuming calcium-rich foods or vitamins within 2 hours of their dose. As always, this medication should be taken with plenty of water to reduce risk of nausea and esophagitis. Recipients may develop photosensitivity.
- There is a concern that doxycycline PEP may result in the development of drug-resistant microbes such as methicillin-resistant *Staphylococcus aureus* and *Neisseria gonorrhea*. While colleagues at CDC grapple with this public health question, clinicians talking with their patients should balance this theoretic issue with the potential harms (including accelerated drug resistance) associated with the increased overall antibiotic consumption among those who develop bacterial STIs.

DISCLOSURE

Dr P.S. Pottinger has nothing to disclose. Dr D.J. McCulloch has nothing to disclose.

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